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Signed Andrew Gerrey

Dated 8 March 1999

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Request for grant of a patent

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9806939.6

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1. Your reference

   CM1737F/NGC

2. Patent application number
   (The Patent Office will fill in this part)

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   The Procter & Gamble Company
   One Procter & Gamble Plaza
   Cincinnati, Ohio 45202, U.S.A.

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation — United States of America 00792 673001.

4. Title of the invention

   A Spray Device

5. Name of your agent *(if you have one)*

   Maxim Courtney Brooks

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Patent Department
   Procter & Gamble Technical Centres
   Lovett House, Lovett Road
   Staines, TW18 3AZ, Middlesex

   Patents ADP number *(if you know it)* 055 388 71005

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

   Yes

A SPRAY DEVICE

Field of the Invention

The present invention relates to a spray device, particularly to a device adapted to produce a spray comprising a fluid ligament with a spray cone diverging from one end of the ligament. More particularly, the invention relates to an electrostatic spray device capable of delivering a soft spray to the nasal cavity without needing to be inserted into the nostrils. The invention further relates to a method of administering a fluid to the nasal cavity from a spray device without substantial penetration of the device into the nostrils. More especially, the invention relates to a method of electrostatically spraying a liquid in such a way that the liquid is initially projected from a spray head in the form of a ligament which enters the nostrils and thereafter breaks up into droplets under the influence of Coulombic forces to produce an atomised spray.

Background of the Invention

Treatment of maladies affecting the nasal region, such as hay fever or congestion due to colds, has long been effected by means of a nasal spray device. More recently it has been recognised that the mucous membranes of the nasal cavity can be used as a convenient delivery site for drugs targeted at other areas of the body. See for example WO 92/11049 which discloses a pen shaped device for nasal administration of, particularly, insulin. Invariably, however, devices for administration of fluids into the nose have been designed such that the device must be partially inserted into the nostrils to be effective. Not only is the manner of using such a device potentially unhygienic and/or uncomfortable for the user, it is often required that the user tilt his or head backwards to avoid the fluid running out of the nose once dispensed.

The nasal cavity is a difficult area of the body to target with drugs. To reach the inner nasal cavity, the drug must be introduced into the vestibule of the nose via the nostrils, travel to the back of this cavity and then pass through the narrow slit-shaped opening of the nasal valve. Once through the nasal valve, the drug then needs to be distributed onto the vascular tissues of the inferior and middle turbinates. The turbinates are finger-like projections of erectile tissue covered with ciliated epithelium and goblet cells. When the nose becomes congested, the turbinates expand and close off the air passages. To be effective, topical drugs such as decongestants, anti-inflammatories, or antihistamines

Summary of the Invention

According to the present invention there is provided a packaged spray device, suitable for spraying into a bodily cavity, the device comprising a spray generator, a fluid reservoir and a nosepiece wherein:

i) the fluid reservoir contains a pharmaceutically acceptable fluid, the fluid comprising a pharmaceutically acceptable treatment agent selected from medicaments, flavours, salts, surfactants and mixtures thereof; and

ii) the device is adapted to produce a spray having a fluid ligament extending from the nosepiece, the ligament having a nosepiece end and a delivery end, the spray further comprising a spray cone diverging from the delivery end of the ligament; wherein

iii) the ligament has a length of from about 1 to about 20 mm from the nosepiece end to the delivery end.

Preferably the spray device is an electrostatic spray device which charges the spray before entry into the nostrils.

According to a further aspect of the present invention there is provided a method of administering a fluid to the nasal cavity from a spray device, the method comprising spraying the fluid into the nasal cavity without substantial penetration of the device into the nostrils.

Detailed Description of the Invention

Fluids

The spray device of the invention comprises a fluid reservoir containing a pharmaceutically acceptable fluid, the fluid comprising a pharmaceutically acceptable treatment agent selected from medicaments, flavours, salts, surfactants and mixtures thereof. The fluid optionally comprises other adjuvants dissolved or dispersed within it. The fluid can be aqueous or non-aqueous. Suitable aqueous fluids include water and mixtures of water with water-miscible solvents such as glycerol, propylene glycol, or alcohols such as ethanol or isopropyl alcohol. Aqueous emulsions can also be used, either water-in-oil or oil-in water emulsions. Preferably the fluid is an aqueous solution, dispersion or oil-in-water emulsion. Suitable non-aqueous fluids comprise polyethylene glycols, glycerol, propylene glycol, dimethyl isosorbide, silicone oils, ketones, ethers and mixtures thereof.

Although not limited to any particular range of resistivity, the invention has particular application to low resistivity fluids, especially those having a bulk resistivity of less

Antihistamines useful to the present invention include, but are not limited to, fast-acting, histamine H-1 receptor antagonists. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: alkylamines, ethanolamines, ethylenediamines, piperazines, phenothiazines, piperidines. Examples of useful fast acting antihistamines include acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, rocastine, phenindamine or pharmaceutically acceptable salts and mixtures thereof. Other useful antihistamines include terfenadine, azelastine, cetirizine, astemizole, ebastine, ketotifen, lodoxamide, loratadine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or pharmaceutically acceptable salts and mixtures thereof. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 3.0%, more preferably from about 0.01% to about 1%.

The medicament can also be an anti-inflammatory agent such as a corticosteroid. Particularly preferred agents within this class are glucocorticoids selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. When used in the compositions of the present invention, the anti-inflammatory agent is preferably present at a concentration of from about 0.001% to about 0.1%, more preferably from about 0.01% to about 0.1%.

Also useful herein are xanthine derivatives such as caffeine and methylxanthine and the like; antiallergics; mucolytics; anticholinergics; non-opiate analgesics such as acetaminophen, acetylsalicylic acid, ibuprofen, etodolac, fenbuprofen, fenoprofen, ketorolac, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically acceptable salts thereof and mixtures thereof; opiate analgesics such as butorphanol; leukotriene receptor antagonists; mast cell stabilisers such as cromolyn sodium, nedocromil and lodoxamide; and lipoxygenase inhibiting compounds.

Further examples of suitable medicaments can be found in WO97/46243, EP-A-780127, US-A-5,124,315, US-A-5,622,724, US-A-5,656,255 and US-A-5,705,490

Flavours

Various flavouring and/or aromatic components (e.g., aldehydes and esters) can be used in the fluids of the invention. These include, for example, menthol, camphor, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde

Fluids useful in the present invention can also comprise from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. A variety of preservatives including, for example, benzyl alcohol, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, chlorhexidine gluconate, or benzalkonium chloride can be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA as a chelating agent. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

Spray devices and spray characteristics

The spray device will generally comprise a means for controlling the dosage of the dispensed fluid. This can be as simple as an on-off switch which allows the user to control the dosage according to his or her needs. Preferably the spray device is adapted to provide a unit fluid dose, more particularly a unit dose with a volume in the range of from about 1 to about 100 µl, preferably from about 1 to about 20, more preferably from about 5 to about 15 µl. In especially preferred embodiments the device is adapted to provide multiple unit doses of the volumes mentioned. The dose volume is preferably pre-set but it can also be adjusted by the user to a desired volume. The device suitably comprises a reservoir for holding the fluid and a dosing means for selectively delivering a unit dose from the reservoir to the spray generator. The dosing means can be, for example, a metered valve or a syringe pump.

The device is adapted to produce a spray having a fluid ligament, the ligament extending from the nosepiece and having a nosepiece end and a delivery end, the spray further comprising a spray cone diverging from the delivery end of the ligament. By "nosepiece end" is meant the point at which a plane (hereinafter the nosepiece plane) drawn perpendicular to the axis of the ligament and just touching the exterior of the nosepiece would intersect the centre of the ligament. The ligament preferably has a length of from about 1 to about 20 mm, more preferably from about 1 to about 10 mm, yet more preferably from about 2 to about 8 mm, and especially from about 3 to about 6mm from the nosepiece end to the delivery end.

does not acquire a net charge. Alternate arrangements, whereby an alternating voltage is applied, can also be used to prevent charge build-up.

The device is activated to deliver the spray. The ligament of the spray extends through the nostril opening, into the vestibule and preferably to within a short distance of the nasal valve opening, before breaking up to form the spray cone. The device can be constructed simultaneously to dispense two sprays, directed to each of two nostrils. The two sprays can be generated from two separate dosing means or can be provided from a single source such as by using a 'Y' shaped valve to split a single jet into two.

In order to provide clean cut-off at low unit volumes the device preferably comprises an elastomeric, self-sealing exit valve having a fluid side and a delivery side, the valve opening to allow passage of the fluid when pressure is applied to fluid on the fluid side and sealing when the pressure is removed. By "exit valve" is meant that the elastomeric valve is the final dispensing valve and that there are no other elements of the device which mechanically, restrict or modify the flow of the fluid on the downstream side of the valve. In highly preferred embodiments herein the valve is a slit valve. The valve can comprise a single slit or tow or more intersecting slits, to form a cross shape for example. Preferably, however, the valve comprises a single slit. Although the valve can be flat it is preferably dome-shaped by which is meant that a non-planar valve having a recess such as with a hemispherical or frustoconical dome. In preferred embodiments the valve is essentially in the form of a hemispherical dome having a flange along its perimeter so that a collar can be fitted to retain the valve in the device. The diameter of the valve, including the flange, is typically from about 2 to about 6 mm with the dome portion having a diameter of from about 1 to about 4 mm, typically about 2.5mm and a thickness from inside to out of from about 0.5 to about 1.5 mm, suitably about 1 mm. The valve need not be of uniform thickness. In preferred embodiments the valve dome's exterior surface is hemispherical whereas the internal surface is formed with a small flat at the top of the dome where the slit is formed. Suitable slit widths are from about 50 to about 400 μm, preferably from about 150 to about 250 μm. It is to be understood that the slit width refers to the longest dimension of the slit when first created. The term "elastomer" herein refers to a material which is both elastically compressible and elastically extensible. A wide range of elastomers can be used, including but not limited to polyurethanes; chloroprene, butyl, butadiene and styrene-butadiene rubbers, and silicone elastomers such as 2 part room temperature vulcanising (RTV) silicones. Preferred for use herein are the 2 part silicone RTVs. Suitable silicone RTVs are available under the trademark NuSil and have a hardness of from about 30 to about 80 Shore A, preferably from about 40 to about 70 Shore A. The elastomers can optionally be mixed with a suitable plasticiser or foaming agent to make

a particle size of 10 μm or less is desirable so that the particles are not carried through into the lungs. It is believed, however, that having an electrostatic charge on the spray particles makes them much less likely to be carried beyond the nose since the charged particles tend to find an earthed surface rather quickly.

The clean stop performance of the tip valve can be further improved by introducing a pressure relief feature behind the valve. This would take the form of a by-pass to the fluid reservoir so that any residual fluid pressurised by relaxation of the elastomer would return to a reservoir rather than dripping from the valve exit.

If necessary, several self-sealing valves can be used in tandem to achieve higher volume throughputs whilst retaining the advantageously small spray particle sizes. The seals from which the valves are made can conveniently be manufactured by a conventional injection moulding process.

Methods

The spray device herein is suitable for spraying into a bodily cavity, particularly into the nose, mouth or ears of a human. The low volume and gentle spray also make it suitable for e.g. ophthalmic spraying. Preferably the device is a nasal spray device. A preferred method of administering a fluid to the nasal cavity from the spray device comprises spraying the fluid into the nasal cavity without substantial penetration of the device into the nostrils. By "without substantial penetration into the nostrils" herein is meant that there is no insertion of a nozzle or such-like into the nasal vestibule. In use, the nosepiece of the device is preferably placed in contact with the nostril opening to obtain the full benefit of the field intensifying effect described herein in relation to the nosepiece. If pressure is applied by the user, for certainty of contact or to assist in orientation there may be some flaring of the nostril or overlap with the septum cartilage but nevertheless the nosepiece will not be completely surrounded by the nostril.

The invention will now be described by way of example only, with reference to the accompanying drawings in which:

Fig. 1 is a sectional view through a human nose.

Fig. 2 is a perspective view of a spray device according to the invention.

Fig. 3 is a greatly simplified sectional view of the spray device of Figure 2 showing the relationship of the elastomeric nozzle to the nosepiece and dosing means.

Fig. 4 is a schematic part section showing a spray issuing from a device according to the invention.

Examples

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention.

Example I

A fluid of the present invention is prepared by combining the following components utilising conventional mixing techniques similar to that described below.

Component	Wt %
oxymetazoline hydrochloride	0.31
sodium citrate dihydrate	1.75
citric acid	0.35
Tyloxapol	0.70
chlorhexidine digluconate	0.054
benzalkonium chloride	0.02
camphor	0.04
eucalyptol	0.02
disodium EDTA dihydrate	0.01
distilled water	q.s. 100ml

In an appropriately sized vessel, the above listed ingredients are added one at a time to water with mixing, allowing each to dissolve before adding the next. After all the ingredients have been added, purified water is used to bring the batch to the appropriate weight. The solution has a bulk resistivity of 120 ohm.cm. The solution is charged into a flexible laminate reservoir and fitted into an electrostatic spray device of the kind indicated in figure 2. The nosepiece of the device is held against the nostril and the device directed such that the spray ligament will enter the nostril. On actuation of the device, 8 µl of the solution is dispensed over a period of about 1 second. The dispensed fluid provides relief from nasal decongestion without causing noticeable wetness either on or inside the nose. The low dose volume and gentle delivery have the result that the user does not sense any appreciable physical impact from the spray.

Example II

A further fluid is prepared by combining the following components utilising conventional mixing techniques similar to that described in Example I.

CLAIMS

1. A packaged spray device, suitable for spraying into a bodily cavity, the device comprising a spray generator, a fluid reservoir and a nosepiece wherein:

   i) the fluid reservoir contains a pharmaceutically acceptable fluid, the fluid comprising a pharmaceutically acceptable treatment agent selected from medicaments, flavours, salts, surfactants and mixtures thereof; and

   ii) the device is adapted to produce a spray having a fluid ligament extending from the nosepiece, the ligament having a nosepiece end and a delivery end, the spray further comprising a spray cone diverging from the delivery end of the ligament; wherein

   iii) the ligament has a length of from 1 to 20 mm from the nosepiece end to the delivery end.

2. An electrostatic spray device according to Claim 1.

3. An electrostatic spray device according to Claim 2 wherein a voltage in the range from 1 kV up to 10 kV is applied to the fluid.

4. A spray device according to any of Claims 1 to 3 wherein the spray cone has a cone angle of from 10 to 90°, preferably 20 to 50°, more preferably from 30 to 40°.

5. A spray device according to any of Claims 1 to 4 wherein the device is adapted to provide a unit fluid dose with a volume in the range from 1 to 20, preferably from 5 to 15 µl.

6. A spray device according to Claim 5 wherein the device is adapted to provide multiple unit fluid doses.

7. A method of administering a fluid to the nasal cavity from a spray device, the method comprising spraying the fluid into the nasal cavity without substantial penetration of the device into the nostrils.

8. A method according to Claim 7 wherein the device sprays simultaneously into two nostrils.

9. A method according to Claim 7 or Claim 8 wherein the device is adapted to provide a unit fluid dose with a volume in the range from 1 to 20, preferably from 5 to 15 µl.

10. A method according to any of Claims 7 to 9 using a device according to any of Claims 1 to 6.

Fig. 1

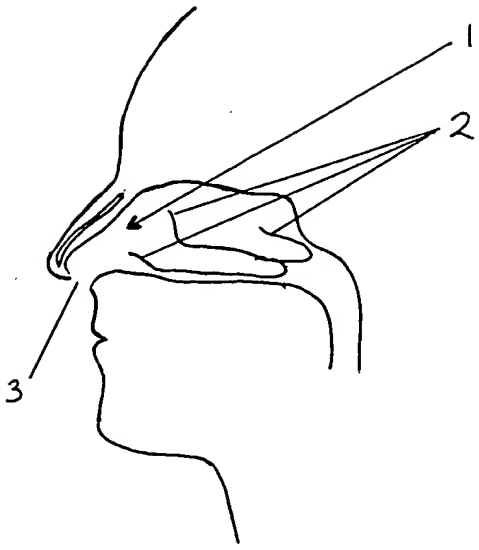

Fig. 2

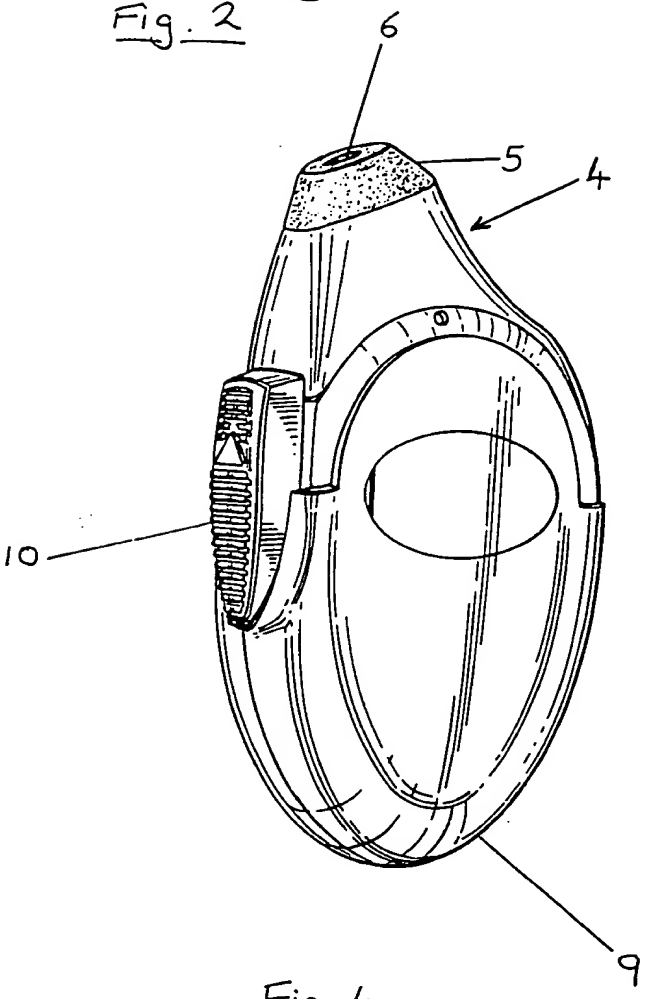

Fig. 3

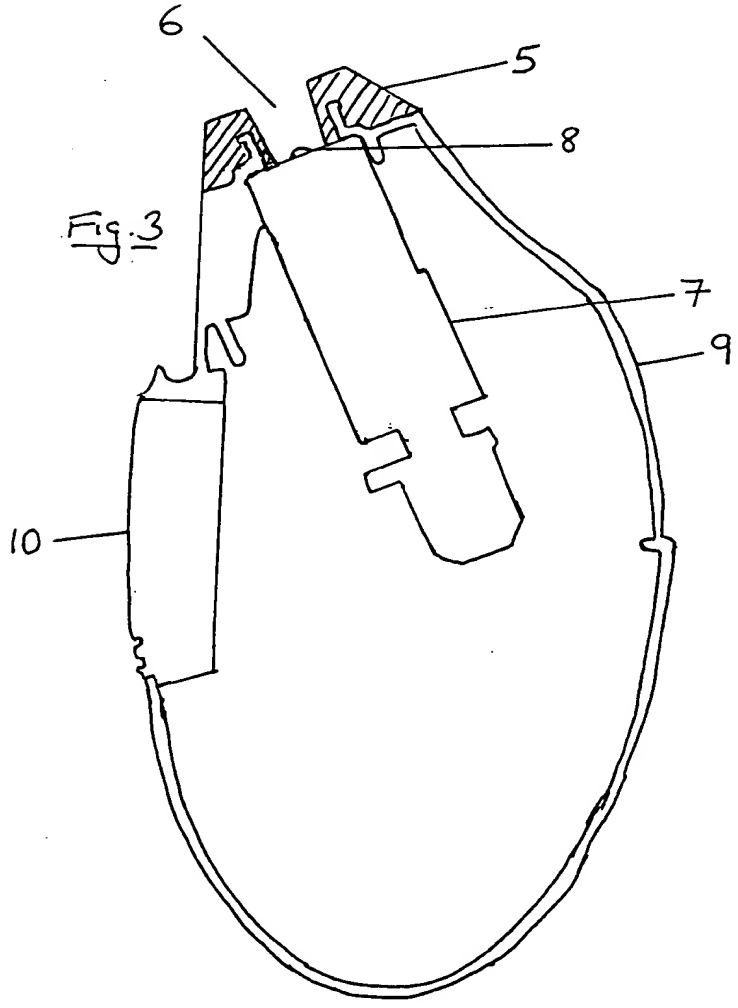

Fig. 4

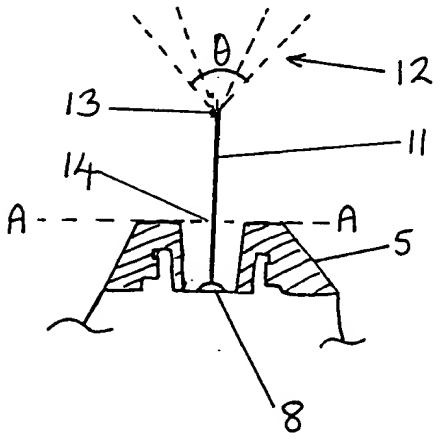

Fig. 5